

Self-healing juvenile cutaneous mucinosis

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Abstract

Girl, aged 4 years old, began the disease with pain of the lower extremities, fever up to 38°C and signs of upper airway infection. Then the patient developed oedema and redness of the whole face, thickened skin, subcutaneous nodular foldings of the frontal, occipital, cervical and axillary regions, extensor areas of the joints; fine, hard whitish nodules in the frontal region and over interphalangeal joints of the hands, pruritus; oedemas of the ankles, knees and joints of the hands, cervical lymphadenopathy and hepatomegaly. Blood tests at the moment of the diagnosis revealed elevation of markers of inflammation as ESR and CRP, leukocytosis, thrombocytosis, hypoalbuminemia, and hyper-alfa-2-globulinemia. Histopathological examination of the skin biopsy specimen and subcutaneous tissue revealed myxoid subcutaneous tissue located under the dermis and a section consisting of myxoid mesenchymal tissue with inflammatory infiltration by histiocytic cells. The presence of acid mucopolysaccharides in fields of the myxoid tissue was also observed. The self-healing juvenile cutaneous mucinosis (SJCM) was diagnosed.

Key words: self-healing juvenile cutaneous mucinosis, lichen myxedematous, mucin deposits, papular or nodular eruption on the skin.

Introduction

Self-healing juvenile cutaneous mucinosis (SJCM) is an extremely rare disease which occurs in childhood or adolescence. It was separated from the lichen myxedematous (LM) group classified as idiopathic cutaneous mucinosis. The terms LM and papular mucinosis are used as synonyms. The first classification of LM was created by Montgomery and Underwood in 1953 [1]. In 2001, Rongioletti and Rebora [2] presented a new LM classification. They distinguished 3 forms of the disease:

- generalized papular form with skin sclerosis – scleromyxoedema,
- localized forms,
- atypical forms.

Generalized LM, scleromyxoedema, is a rare chronic sclerodermoid disease showing no tendency for spontaneous resolution. Symptoms usually develop between the third and seventh decade of life [2, 3]. Two types of

skin lesions are observed: fine waxy papules localized behind the ears, on the auricle and forehead, plus sclerotic foci arranged in folds, especially on the trunk and peri-articular area. Diagnosis is based on clinical symptoms (presence of papular and sclerodermoid eruptions), typical histopathological examination (presence of mucin deposition, fibroblast proliferation, fibrosis), and laboratory findings (monoclonal gammopathy). It is necessary to exclude any thyroid disease. Scleromyxoedema can intercurrent with diseases of the hematopoietic system (multiple myeloma, Hodgkin's disease, leukemia), myopathies (myositis, dermatomyositis), lesions in the central nervous system, peripheral neuropathies, and psychiatric diseases [4].

Localized LM forms are subdivided into the following subtypes [2]:

- discrete papular form,
- persistent papular mucinosis,

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- self-healing papular mucinosis, juvenile type (SJCM),
- self-healing papular mucinosis, adult type,
- papular mucinosis of infancy,
- nodular form.

Diagnosis criteria of LM localized forms are the following: the presence of papular or modular eruption on the skin, clinically confirmed, mucin deposits with variable fibroblast proliferation upon histopathology examination, and the absence of thyroid diseases or monoclonal gammopathy.

Due to its rare incidence, SJCM, one of localized forms of LM, can cause significant diagnostic problems to pediatricians.

Case report

Girl, aged 4 years old, born from healthy parents with non-contributory gestational and perinatal history. History of left heminephrectomy in 2009 (infancy) due to pelvicalyceal duplication of the left kidney.

The disease started suddenly with pain in the lower extremities – the child refused to walk. On the next day, fever up to 38°C occurred which responded well to antipyretic medications, plus symptoms of an upper airway infection, and oedema of both talar joints appeared. The girl was hospitalized at Pediatric Ward of Regional Hospital where she was diagnosed with symptoms of nasopharyngitis, oedemas of talar joints. Blood tests showed elevated inflammatory markers values: ESR 40 mm/h, CRP 37.3 mg/l, leukocytosis, with normal serum procalcitonin levels, and increased total IgE and IgA levels. Several infection factors including tuberculosis were eliminated. Antinuclear antibodies (ANA) and rheumatoid factor (RF) was not detected. Ultrasound examination of talar joints revealed trace exudates with no lesions in the synovial membrane. The girl was treated with cefuroxime, clarithromycin and non-steroid anti-inflammatory drugs. Regarding articular pains, short-lasting improvement was obtained, but, fever and upper airway infection symptoms receded. From the 7th day of hospitalization, skin lesions were observed to spread, in the form of subcutaneous nodules on the head, in the axillary regions, over proximal interphalangeal joints of hands, facial oedema also occurred. From the 11th day, micropapular lesions on the face were observed. Diagnosed with arthritis, atopy and subcutaneous nodules of unknown etiology, the girl was directed to Clinic of Developmental-Age Rheumatology, Institute of Rheumatology.

Upon the admission the child's condition was assessed as medium-severe.

Abnormalities revealed on physical examination included mainly the following skin lesions accompanied by intensive pruritus:

- oedema and redness of the whole face,
- oedema/thickened skin, or subcutaneous nodular foldings of the frontal, occipital and cervical and axillary regions, and extensor areas of the elbows, wrists and knees,
- numerous, fine and quite hard whitish nodules in the frontal region and over interphalangeal joints of the hands.

Physical examination revealed also oedemas of the talar and knee joints, and fine joints of the hands, as well as palpable fine cervical lymph nodes, and hepatomegaly.

Laboratory tests showed slightly elevated inflammatory markers: ESR 52 mm/h, CRP 24 mg/l, leukocytosis, thrombocytosis, hypoalbuminemia, and hyper- α 2-globulinemia.

Thyroid diseases were excluded. No specific antibodies (RF, ANA, p-ANCA, c-ANCA, cryoglobulins) or immune complexes were detected. Electrocardiography (ECG) and transthoracic echocardiography did not show any abnormalities. Ultrasound examination of knee joints revealed a minor exudate with distinct thickening and single vascularity of synovial membrane bilaterally. Ultrasound scan of the right talar joint did not reveal any abnormalities.

Treatment included antibiotic therapy (amoxicillin with clavulanic acid, followed by ciprofloxacin and fluconazole), and anti-histamine drugs. From the 2nd day of hospitalization, due to intensive pruritus and oedema of eyelids, nasal root and soft tissues, the girl received intravenous infusion of methylprednisolone in an initial dose of 2 mg/kg followed by 4 mg/kg body mass/daily.

Applied medication led to normalization of inflammatory markers. However, no clinical improvement was achieved regarding skin lesions: moreover, new nodules which were fine, quite hard, whitish, making linear arrangements on the trunk, with persistent pruritus appeared. The skin lesions were accompanied by medium-severe articular symptoms: limited joint mobility of elbows and wrists, trace patellar ballottement in both knees, transient oedema of talar joints.

Control USG of knee joints, right talar joint and right wrist did not reveal any inflammatory lesions or other abnormalities.

During further diagnostics, hematological and oncological consultations excluded any proliferative disease. Biopsy of the skin and subcutaneous tissue was performed: material from two lesions was collected – from a subcutaneous nodule in the occipital region, and a micronodule over the proximal interphalangeal joint of the hand. Histopathological examination included a skin section with a small amount of myxoid subcutaneous tissue located under the dermis, and a section consisting of myx-

oid mesenchymal tissue with inflammatory infiltration by histiocytic cells. As the appearance was ambiguous, it allowed to preclude a malignant process, rheumatoid nodule, tuberculosis, mycosis; it might be suggestive of multiple myxoma, or a reactive lesion; *in situ* hybridization (ISH) did not reveal any elements of CMV genome. Additionally, staining method was applied and revealed the presence of acid mucopolysaccharides in fields of the myxoid tissue.

Basing on the clinical presentation and additional examinations, SJCM was diagnosed. It was not however possible to definitely exclude the initial stage of juvenile idiopathic arthritis (articular oedemas, lesions visible in ultrasound scan of knee joints, elevated inflammatory markers, resolution of the symptoms upon glucocorticoid steroid (GCS) therapy.

Following therapy included gradually reduced daily doses of GCS, then – switching to oral dosage form – prednisone. While the doses were tapered down, the child remained in good condition, without fever or pain complaints, and periodic pruritus episodes responded to antihistamine and sedative treatment.

Then, the child was followed up at Rheumatology Outpatient Clinic, after 4 months, the GCS therapy was terminated.

When the treatment was complete, the child's condition did not deteriorate, and gradual regression of the skin lesions was observed until they definitely receded at 8 months from the onset. During the over two years' ambulatory follow-up, inflammatory lesions of joints did not reoccur, laboratory tests results were normal, and control ultrasound scans did not reveal any abnormalities. As an outpatient, the child was consulted by endocrinologist, dermatologist, immunologist and geneticist. The consultants excluded any diseases from their scopes of specialization.

The long-term observation allowed to confirm the diagnosis of SJCM, and to exclude juvenile idiopathic arthritis (JIA).

Discussion

Self-healing juvenile cutaneous mucinosis was first described in France in 1973 [5]. The cause of the disease remains unknown.

Among the thirteen SJCM patients described in the literature, the age at onset was between 13 months to 15 years [6]. The onset was always abrupt. In five cases, skin lesions were not accompanied by any other symptoms, in one case – they were preceded by upper airway infection symptoms, and sporadically, skin lesions were secondary to nephroblastoma and carpal tunnel syndrome. The following accompanying symptoms were reported: pains and oedemas of joints (knees, elbows, hands), muscle pains, fever, general weakness, sclerotic

oedema of the face. Laboratory abnormalities included accelerated ESR, lymphocytosis, increased aldolase levels, presence of antibodies against *Bartonella* (two cases) [6], and signs of myositis and oedema of the subcutaneous tissue upon MRI examination (one case).

Classically, 3 types of skin lesions are reported in SJCM:

- non-tender ivory papules on the head, neck, trunk, periarticular regions; arranged linearly on the chest and abdomen,
- subcutaneous nodules on the head and in periarticular regions,
- hard periorbital and zygomatic oedema [6–9].

Periarticular lesions most often occur in the regions of knee, elbow and hand joints.

Typical histopathological presentation includes:

- oedema of the dermis,
- moderate fibroblast proliferation,
- benign perivascular cell infiltration,
- positive test of alcian blue (also called Ingrain blue 1) staining at pH 2.5: confirmed presence of mucopolysaccharide acid (mucin) [6, 7].

The disease resolves spontaneously, however, duration of symptoms in described cases varied from several weeks to 2.5 years.

In our patient's age at the disease onset and the abrupt onset of the disease with the accompanying upper airway infection are not different from cases described in the literature. What is most important, however, the presentation of skin lesions is consistent with the three classic types of lesions within the skin. Symptoms presented by our patient, i.e. articular pains and oedemas, and laboratory abnormalities (increased ESR) are also confirmed in other reported cases of children. However, there have been no reports of intense pruritus within the pathologically changed region of the skin, which was predominant at the initial stage of the disease in our patient. It was suggestive of allergic skin lesions, and made us initiate GCS therapy. Clinical diagnosis of SJCM is usually confirmed by the presence of mucin deposition within the myxoid tissues of collected skin sections. Among all reported SJCM cases, only some authors include description of histopathological examination of collected skin lesions, and such histopathological descriptions vary. Wade et al. [10] mentioned the presence of mucin in the medium and deep layers of the dermis, together with distinct fibroblasts.

Cowen et al. [6] described intense lesions in the subcutaneous tissue, and minor mucin deposition in the dermis; it should be stressed that skin lesions typical of mucinosis that were reported by the authors in their described case were accompanied also by lesions suggestive of erythema nodosum. Nagaraj et al. [7] described 3 cases of SJCM.

In all the cases, histopathological examination revealed the presence of various inflammatory cells within the myxoid stroma containing mucin deposition. Histopathological evaluation in the case of our patient included two affected areas: a skin section with some myxoid subcutaneous tissue localized under the dermis, and a section consisting of myxoid mesenchymal tissue with inflammatory infiltration by histiocytic cells, with a positive staining test for the presence of mucin.

Differential diagnostics of SJCM includes mainly dermatological diseases.

Infantile papular mucinosis was excluded because of our patient's age at the onset. Mucinosis caused by consumption of toxic oil was excluded on the basis of medical history. The clinical presentation did not correspond with scleromyxoedema due to the age at onset, absence of sclerosis of fingers, absence of monoclonal gammopathy, absence of increased collagen levels upon histopathological examination, and finally, due to spontaneous resolution of the disease.

The history-taking allowed also to exclude scleroderma – no documented history of streptococcal infection, diabetes, monoclonal gammopathy, inconsistent histopathology findings. The presence of accompanying symptoms in our patient made it necessary to differentiate between SJCM and rheumatic diseases of the developmental age. Articular pains and oedemas, signs of inflammatory process generalization in the form of fever, elevated inflammatory markers, and lesions visible in the ultrasound scan of joints suggested juvenile idiopathic arthritis. Such a diagnosis seemed to be confirmed by good response to the applied

GCS therapy when fever and joint lesions were resolved, and inflammatory markers returned to normal values. During the 9-month follow-up period after GCS discontinuation, fever and arthritis symptoms did not reoccur. Facial oedema and redness as well as lesions over hand joints may be also suggestive of juvenile dermatomyositis. Here, the discriminative factor was the absence of muscle involvement, confirmed both clinically and by evaluation of muscle enzymes activities.

Systemic scleroderma was excluded on the basis of clinical presentation (not only skin sclerosis but papular lesions as well), and histopathology findings.

Summary

Self-healing juvenile cutaneous mucinosis is a rare disease, causing major diagnostic problems. Due to accompanying symptoms, it may require rheumatological diagnostics. The key diagnostic tool is histopathological evaluation of the skin lesions. No effective treatment method of the disease is available yet.

The disease resolves spontaneously, without permanent consequences, so the prognosis in self-healing juvenile cutaneous mucinosis should be deemed as good.

The authors declare no conflict of interest.

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